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Changes in Pulmonary Function and Airway Reactivity Due to Prolonged Exposure to Typical Ambient Ozone (O3) Levels

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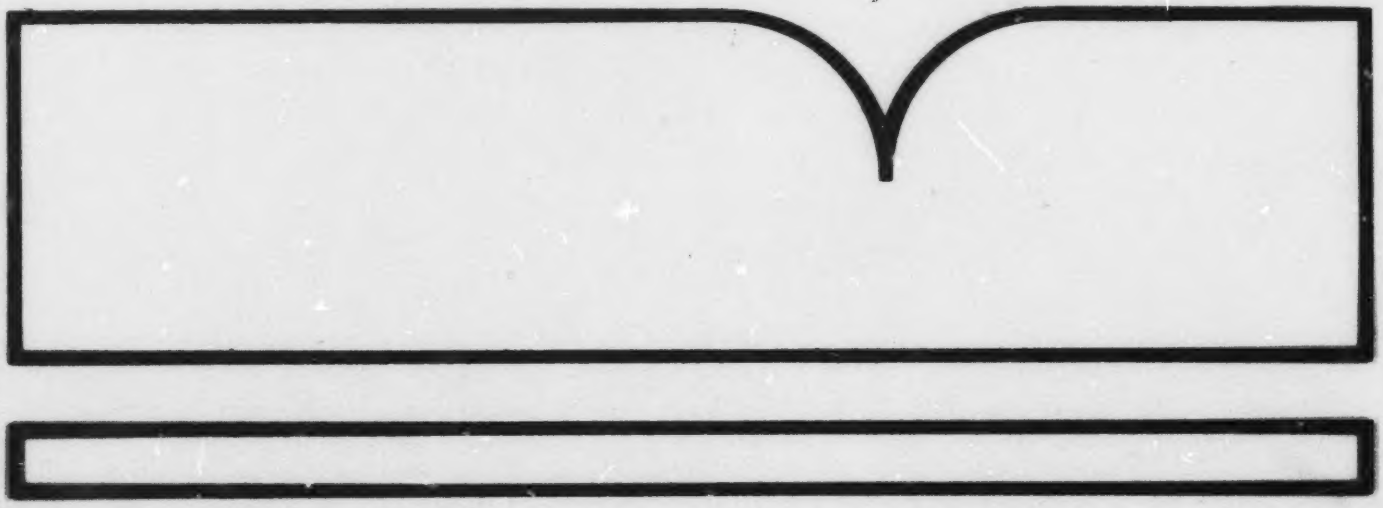

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Previously observed (JAPCA 38:28-35, 1988) pulmonary responses of ΔFEV_1 (-13%), moderate to severe pain upon inspiration, and a doubling of PD_{100} for methacholine following prolonged moderate exercise at 0.12 ppm O_3 were of sufficient magnitude to warrant our assessing responses at a lower range of concentrations, i.e., 0.08, 0.10 and 0.12 ppm O_3. Exposures consisted of six 50-min exercises ($\dot{V}_E$ ≈40 L/min), each followed by 10-min rest; a 35-min lunch break was included. When compared with exposures to 0.00 ppm, substantial pulmonary function decrements, respiratory symptoms and increases in nonspecific airway reactivity were observed at all three O_3 concentrations. For example, decreases in FEV_1 ($P < 0.01$) of 7%, 7% and 12% were observed at 0.08, 0.10 and 0.12 ppm O_3, respectively. The ratios ($P < 0.005$) of PD_{100} observed in 0.00 ppm to that in O_3 were 1.56 at 0.08 ppm, 1.89 at 0.10 ppm, and 2.21 at 0.12 ppm O_3. We conclude that exercise representative of a day of moderate to heavy work or play performed during exposures to O_3 at levels and pattern often found in ambient air induced clinically meaningful pulmonary responses.

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CHANGES IN PULMONARY FUNCTION AND AIRWAY REACTIVITY DUE TO PROLONGED EXPOSURE TO TYPICAL AMBIENT OZONE (O_3) LEVELS

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ABSTRACT

Previously observed (JAPCA 38:28-35, 1988) pulmonary responses of ΔFEV_1 (-13%), moderate to severe pain upon inspiration, and a doubling of PD_{100} for methacholine following prolonged moderate exercise at 0.12 ppm O_3 were of sufficient magnitude to warrant our assessing responses at a lower range of concentrations, i.e., 0.08, 0.10 and 0.12 ppm O_3. Exposures consisted of six 50-min exercises ($\dot{V}_E$ ≈40 L/min), each followed by 10-min rest; a 35-min lunch break was included. When compared with exposures to 0.00 ppm, substantial pulmonary function decrements, respiratory symptoms and increases in nonspecific airway reactivity were observed at all three O_3 concentrations. For example, decreases in FEV_1 ($P < 0.01$) of 7%, 7% and 12% were observed at 0.08, 0.10 and 0.12 ppm O_3, respectively. The ratios ($P < 0.005$) of PD_{100} observed in 0.00 ppm to that in O_3 were 1.56 at 0.08 ppm, 1.89 at 0.10 ppm, and 2.21 at 0.12 ppm O_3. We conclude that exercise representative of a day of moderate to heavy work or play performed during exposures to O_3 at levels and pattern often found in ambient air induced clinically meaningful pulmonary responses.

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INTRODUCTION

Daily ambient O_3 levels between 0.08 and 0.12 ppm for periods in excess of 6-hr often occur in many urban, suburban and even rural areas of both the U.S. and Europe (ref. 1). We recently observed substantial decrements in pulmonary functions (eg. ΔFEV_1 = -13%,) moderate to severe respiratory symptoms, and a 2-fold increase in nonspecific airway reactivity when young men performed exercise equivalent to a day of moderate to heavy work or play while exposed to 0.12 as compared to 0.00 ppm O_3 (ref. 2). Specifically, 6.6-hr exposures

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consisted of six 50-min periods of moderate exercise (average V_E = 42.5 L/min), each followed by a 10-min rest; a 35-min lunch period followed the third exercise. The magnitudes of the 0.12 ppm O_3-induced responses clearly indicated that, with similar conditions of exercise-exposure duration and $\dot{V}_E$, pulmonary responses would also occur at lower O_3 concentrations. The purpose of this study was to evaluate pulmonary responses resulting from such exposures to 0.08, 0.10 and 0.12 ppm O_3.

METHODS

Healthy nonsmoking male volunteers (n = 22) were subjects in this study. They were recruited from the Chapel Hill, Durham, and Raleigh North Carolina area, which has relatively clean air. Potential subjects were excluded from participation if they had a history of cardiac disease, allergic rhinitis, asthma, or other chronic respiratory disease; if they were routinely exposed to dusty, caustic or pollutant environments; or if they had participated in our previous prolonged O_3 exposure study (ref. 2). Subjects accepted for study were also required to be at least moderately active (i.e. they participated in some form of regular exercise) so that they could sustain a prolonged period of moderate exercise. Health status of potential subjects was assessed by medical history, physical examination, and routine hematologic and biochemical tests. The average subjects' age, height and weight were 24.5 yr, 180.2 cm and 77.0 kg, respectively. The average baseline FVC (5.6 L, range = 3.6-7.9 L) and FEV_1 (4.4 L, range = 2.9-5.3 L) for these subjects were consistent with values predicted from two reference standards (refs. 3,4). However, their FEV_1/FVC averaged 79% as compared to a predicted ratio of 84%.

Prior to participation in the study, subjects were informed of the purpose, design, risks and benefits of the study and signed a statement of informed consent. The study protocol and consent form were examined and approved by the University of North Carolina School of Medicine Committee on the Protection of the Rights of Human Subjects. Each subject participated in training session during which he was instructed as to the performance of pulmonary function tests. At this time, the exercise intensity required to elicit a $\dot{V}_E$ of 8 L/min per liter of FVC, but not less than 35 L/min nor greater than 45 L/min, was also determined for both treadmill and cycle ergometers.

Each subject was exposed to 0.00 (filtered air), 0.08, 0.10 and 0.12 ppm O_3 on separate days. Exposures were separated by a minimum of one week and the exposure sequence was randomized. Neither subjects nor staff directly involved in conduct of exposures and pulmonary testing were informed as to the presence or concentration of O_3 in the chamber although the odor of O_3 was detectable even at these low concentrations. Although it was not possible to have either single or double blind conditions regarding the presence or absence of O_3, the subjects were probably unable to distinguish among the three O_3 concentrations.

Subjects were exposed in pairs when possible.

Upon arrival at the laboratory, each subject was given a brief physical examination. They were not studied if they presented with any condition which contraindicated exposure or exercise, or if they reported an acute respiratory infection within the previous four weeks. Forced expiratory spirometry was measured and pain upon deep inspiration (PDI) was evaluated before (baseline) and after all exposures. Following baseline measurements, the subject entered the chamber, which was already set at the appropriate exposure conditions, and began exercise on either a treadmill or a cycle ergometer at the previously determined exercise intensity. During each exposure, the subject performed six 50-min periods of exercise, alternating between the treadmill and cycle ergometer; five of the 50-min exercises were followed by a 10-min rest, while a 35-min lunch period followed the third exercise. During each exercise period we measured $\dot{V}_E$, oxygen consumption ($\dot{V}O_2$) and heart rate (HR) for 3-min after 40-min of exercise. To assess nonspecific airway reactivity, a methacholine inhalation challenge was performed 15- to 20-min after the 6.6-hr exposure.

Exercise $\dot{V}_E$ (BTPS), $\dot{V}O_2$ (STPD) and HR were derived as described previously (ref. 5); HR and electrocardiogram were continually monitored throughout exposure. Forced expired vital capacity (FVC) was measured in triplicate on a 12-liter dry-seal spirometer; volumes were corrected to BTPS. From the FVC maneuver, expired volume during the first second (FEV_1) was determined and the largest FEV_1 (of the three) was used in the data analysis. PDI was evaluated on the 5-point scale: 0 (none), 1 (just noticeable), 2 (mild discomfort), 3 (moderate discomfort), and 4 (severe discomfort or pain).

Methacholine bronchial challenge procedures conformed to previously published American Thoracic Society guidelines (ref. 6) and were essentially the same as that previously reported for this laboratory (ref. 7). Briefly, methacholine aerosols (MMAD = 1.8 micron, geometric S.D. = 1.4) were generated from solutions of methacholine chloride dissolved in normal saline using an ultrasonic nebulizer; methacholine concentrations were 0.0, 0.63, 1.25, 2.5, 5.0, 10.0, and 20.0 mg/ml. The aerosol was inhaled through a heated Fleisch pneumotach. A microprocessor controlled device was used which both measured and regulated the tidal volume (V_t) such that V_t was approximately 25% of FVC; end-inspiratory breath-hold time was 4-sec and inspiratory flow was between 300 and 500 ml/S. Beginning with normal saline alone and followed by progressively increasing methacholine concentrations, a series of aerosol inhalations was performed. Each consisted of five breaths of aerosol followed by two measurements of airway resistance, beginning 2-min after the start of aerosol inhalation. This sequence of aerosol inhalation and measurement was repeated at 6 minute intervals until the SRav was at least double that following inhalation of saline alone. Airway reactivity to methacholine (prococative dose, PD_{100}), as an indicator of nonspecific airway reactivity, was determined

as the interpolated cumulative dose of methacholine which provoked a 100% increase in SRaw over that observed after inhaling normal saline. Cumulative methacholine dose was expressed as the sum of all doses of inhaled aerosol in cumulative inhalation units (CIU). An inhalation unit was defined as the product of methacholine concentration (mg/ml) and the number of breaths taken at that concentration. Inhalation of one CIU was equivalent to inhalation of 0.035 µg methacholine chloride.

Exposures were conducted in a 4 x 6 x 3.2 m stainless steel chamber with continuous reconditioning and recirculation of the chamber air through high-efficiency particle filters. A detailed description of the chambers and their operating characteristics has been published (ref. 8). Ozone was continuously monitored using chemiluminescent ozone analyzers which were calibrated daily by a Dasibi ultraviolet ozone photometer traceable to an NBS standard photometer. For the four exposure conditions, O_3 concentrations averaged 0.00, 0.08, 0.10 and 0.12 ppm. NO, NO_2, and SO_x were also monitored; their concentrations were routinely less than 0.02 ppm, 0.005 ppm, and 0.005 ppm, respectively. The total particle mass with 3 persons in the chamber was routinely less than 3 $\mu g/m^3$ with 10^5 particles/m^3. The temperature and relative humidity of the chamber were maintained at 22°C and 40%, respectively.

The null hypotheses tested were that (1) there was no difference in the average pre- to postexposure changes in FEV_1 in O_3 as compared to average change in air, and (2) there were no differences in postexposure PDI or PD_{100} in O_3 as compared to those in air. Responses for all three O_3 exposures were compared to air response using a nonparametric version of the Williams' test for randomized block design (ref. 9). Williams' test is appropriate for comparisons of multiple treatments to a control when treatment is either an increasing or decreasing monotonic function. The nonparametric version of the test was used because the assumptions of equal variances of errors and normal distribution of errors (required for application of parametric tests) were not valid for these data.

RESULTS

All but one subject completed all four 6.6-hr chamber exposures. This subject was not exposed to 0.12 ppm because he experienced severe respiratory symptoms at 0.10 ppm O_3, although the magnitudes of his pulmonary function responses only slightly exceeded the mean responses at 0.08 and 0.10 ppm O_3. None of his data were used in the statistical analyses, nor was it included for calculation of the mean data reported later in this section.

The treadmill exercise was a brisk walk ($\bar{X}$ = 3.27 mph) up a slight incline ($\bar{X}$ = 5.7%), while the bicycle exercise was light to moderate ($\bar{X}$ = 72 watts). There were no differences among the four exposures for the means of HR, $\dot{V}_E$ and $\dot{V}O_2$ obtained during any of the six exercise periods. Mean HR (beats/min), $\dot{V}_E$

(L/min) $\dot{V}O_2$ (L/min) averaged over the six exercises were, respectively; 115, 38.5 and 1.53 L/min at 0.00; 116, 39.4 and 1.60 L/min at 0.08; 115, 38.7 and 1.56 L/min at 0.10; and 113, 38.7 and 1.64 L/min at 0.12 ppm O_3.

The preexposure mean values of all of the pulmonary functions measured were quite similar at the four O_3 concentrations and the range of individual subject's coefficients of variation for any of the preexposure measurements of function was quite narrow. For example, FEV_1 averaged 4.40, 4.39, 4.38 and 4.38 L/min prior to exposures to 0.00, 0.08, 0.10 and 0.12 ppm O_3, respectively, while the mean and median individuals' coefficients of variation for FEV_1 were 2.30 ± 0.34% and 2.09%, respectively. Significant O_3-induced responses were observed at all three O_3 concentrations for the three variables tested in the statistical analyses. While essentially no change (+0.6%) was observed for FEV_1 at 0.00 ppm, it was significantly ($p < 0.005$) decreased by 7.0%, 7.0% and 12.3% following exposures to 0.08, 0.10 and 0.12 ppm O_3, respectively. Average ratings of PDI were low, but significantly increased ($P < 0.05$) following exposure to all three O_3 concentrations, i.e., 0.62 at 0.08, 0.90 at 0.10 and 1.00 at 0.12 as compared to 0.24 at 0.00 ppm O_3. O_3-induced increases ($P < 0.005$) in nonspecific airway reactivity were observed at all three O concentrations. The average ratios of PD_{100} observed in 0.00 ppm (57.5 CIU) to those observed in O_3 were 1.56, 1.89 and 2.21 at 0.08, 0.10 and 0.12 ppm O_3, respectively. A wide range of individual responsiveness was exhibited for all variables measured. For example, individual FEV_1 responses ranged from +6.4 to -4.6% at 0.00, from +7.9 to -25.9% at 0.08, from +2.0 to -22.0% at 0.10 and from +2.8 to -38.9% at 0.12 ppm O_3.

DISCUSSION

Our results clearly demonstrate that substantial pulmonary responses occur when 5-hr of moderate exercise is performed during 6.6-hr exposures to 0.08, 0.10 and 0.12 ppm O_3. The consistency of individual preexposure measurements of pulmonary functions indicates that the status of the subjects' airways and the accuracy of measurement was similar prior to exposure at all O_3 concentrations. The large intersubject variability in magnitude of responses which we observed is consistent with results from almost all previous studies of O_3 exposure (eg. refs. 2,5). Individual O_3-responsiveness has been shown to be quite reproducible indicating that intersubject variability is related to differences in individuals' intrinsic responsiveness to O_3 (ref. 10). Thus, our results imply that some individuals will experience substantial pulmonary distress if they exercise (work or play) for prolonged periods at very low O_3 concentrations, while others will not experience any effect from such exposures.

While not intended as an exact simulation, the overall duration, intensity and metabolic requirements of the exercise performed was equivalent to a day of moderate to heavy work or play. The range of HR and $\dot{V}O_2$ we observed was representative of relative exercise intensities between 30% and 45% maximal $\dot{V}O_2$. Moreover, since both HR and $\dot{V}O_2$ drift upvard during prolonged exercise, and since measurements were not obtained until after 40-min of exercise, the actual exercise intensities probably more nearly represented an even lover range of relative effort. There is general agreement that most individuals can comfortably perform prolonged exercise (≈8-hr) at relative exercise intensities ≤ 40% maximal $\dot{V}O_2$, and with lov incidence of fatigue at relative exercise intensities between 40 and 50% maximal $\dot{V}O_2$. It should be noted that, like HR and $\dot{V}O_2$, $\dot{V}_E$ also tends to increase slightly during prolonged exercise and it may be that measured $\dot{V}_E$ also overestimated the actual average exercise $\dot{V}_E$ (ref. 11).

We were not surprised by our earlier findings (ref. 2) of pulmonary responses with the performance of prolonged moderate exercise at 0.12 ppm O_3. Pulmonary function changes and respiratory symptoms had been observed when at least 1-hr of heavy exercise ($\dot{V}_E$ > 60 L/min) was performed during 1-hr and 2-hr exposures to 0.12 ppm O_3 (refs. 5,12,13). Since pulmonary responses at any O_3 concentration are a function of exercise $\dot{V}_E$ and duration (ref. 14), the magnitudes of these variables for our more prolonged exposures to 0.12 ppm O_3 were certainly sufficient to induce responses. Similarly, because the pulmonary responses we observed earlier at 0.12 ppm O_3 were so large, we expected that, with similar conditions of exercise $\dot{V}_E$ and duration, measurable responses would also be induced at 0.10 ppm; we were not sure of what to expect at 0.08 ppm. Thus, we were not surprised by the magnitudes of decrements in pulmonary functions and increases in nonspecific airway reactivity observed at 0.10 ppm, while the magnitudes at 0.08 ppm O_3 were perhaps somevhat greater than we expected. Consistent with our observations, pulmonary function decrements at 0.08 ppm O_3 had been suggested for active children attending summer camps in areas which attained a range of daily ambient O_3 with levels as high as 0.15 ppm throughout the camping session (refs. 15,16,17).

The FEV_1 decrement with exposure to 0.12 ppm O_3 in our current study and those in our earlier study, (ΔFEV_1 ≈ -13%) were remarkably similar. Likewise, an approximately 2-fold increase in nonspecific airway reactivity was observed in both studies. PDI was rated much lower at 0.12 ppm O_3 in the current than in the earlier study; it was also rated lov at 0.10 and 0.08 ppm. We observed essentially no differences in pulmonary function decrements and respiratory symptoms between exposures at 0.08 and 0.10 ppm O_3. We have no explanation for the lov overall symptom ratings, nor for the lack of concentration/response relationships at 0.08 and 0.10 ppm O_3.

PD_{100} did exhibit a concentration/response relationship for all three levels of O_3. This O_3-induced increase in nonspecific airway reactivity is especially interesting since a strong relationship has been reported between increased airway reactivity to cholinergic agonist and increased numbers of neutrophils in bronchoalveolar lavage fluid folloving O_3 exposure (refs. 18-20). Since an increase of neutrophils is a strong indicator of airway inflammation, O_3-induced airway hyperresponsiveness to methacholine may also be a good marker of injury to airway epithelium (ref. 21).

We conclude that substantial pulmonary responses occur following 5-hr of moderate exercise performed during 6.6-hr exposures to 0.08, 0.10 and 0.12 ppm O_3. These findings are particularly relevant to everyday experiences since the intensity, duration and metabolic requirement of the exercise vas representative of a day of moderate to heavy work or play, and the O_3 levels and pattern were similar to ambient levels and pattern often recurring in many areas of both the U.S. and Europe.

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